World Academy of Science, Engineering and Technology
International Journal of Medical and Health Sciences
Vol:16, No:06, 2022

Targeting Matrix Metalloprotease-9 to Reduce Coronary Artery Manifestations of Kawasaki's Disease

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Abstract : Kawasaki disease (KD) is the primary cause of acquired pediatric heart disease as an acute vasculitis. In children with prolonged fever, rash, and inflammation of the mucosa KD must be considered as a clinical diagnosis. There is a persuasive suggestion of immune-mediated damage as the pathophysiologic cascade of KD. For example, the invasion of cytotoxic T-cells supports a viral etiology and the inflammasome of the innate immune system is a critical component in the vasculitis formation in KD. Animal models of KD propose the cytokine profiles, such as increased IL-1 and GM-CSF, which cause vascular damage. CRP and IFN-γ elevated expression and the upregulation of IL-6, and IL-10 production are also described in previous studies. Untreated KD is a critical risk factor for coronary artery diseases and myocardial infarction. Vascular damage may encompass amplified T-cell activity. SMAD3 is an essential molecule in down-regulating T-cells and increasing expression of FoxP3. It has a critical effect in the differentiation of regulatory T-cells. The discrepancy of regulatory T-cells and pro-inflammatory Th17 has been studied in acute coronary syndrome during KD. However in the coronary artery damaged lymphocytes and IgA plasma cells are seen at the lesion locations, the major immune cells in the coronary lesions are monocytes/macrophages and neutrophils. These cells secrete TNF-α, and activates matrix metalloprotease (MMP)-9, reducing the integrity of vessels and prompting patients to arise aneurysm. MMPs can break down the components of the extracellular matrix and assist immune cell movement. IVIG as an effective form of treatment clarified the role of the immune system, which may target pathogenic antigens and regulate cytokine production. Several reports have revealed that in the coronary arteries, high expression of MMP-9 in monocyte/macrophage results in pathologic cascades. Curcumin is a potent antioxidant and anti-inflammatory molecule. Curcumin decreases the production of reactive oxygen and nitrogen species and inhibits transcription factors like AP-1 and NF-κB. Curcumin also contains the characteristics of inhibitory effects on MMPs, especially MMP-9. The upregulation of MMP-9 is an important cellular response. Curcumin treatment caused a reverse effect and down-regulates MMP-9 gene expression which may fund the anti-inflammatory effect. Curcumin inhibits MMP-9 expression via PKC and AMPK-dependent pathways in Human monocytes cells. Elevated expression and activity of MMP-9 are correlated with advanced vascular lesions. AMPK controls lipid metabolism and oxidation, and protein synthesis. AMPK is also necessary for the MMP-9 activity and THP-1 cell adhesion to endothelial cells. Curcumin was shown to inhibit the activation of AMPKα. Compound C (AMPK inhibitor) inhibits MMP-9 expression level. Therefore, through inactivating AMPKs and PKC, curcumin decreases the MMP-9 level, which results in inhibiting monocyte/macrophage differentiation. Compound C also suppress the phosphorylation of three major classes of MAP kinase signaling, suggesting that curcumin may suppress MMP-9 level by inactivation of MAPK pathways. MAPK cascades are activated to induce the expression of MMP-9. Curcumin inhibits MAPKs phosphorylation, which contributes to the down-regulation of MMP-9. This study demonstrated that the potential inhibitory properties of curcumin over MMP-9 lead to a therapeutic strategy to reduce the risk of coronary artery involvement during KD.

Keywords : MMP-9, coronary artery aneurysm, Kawasaki's disease, curcumin, AMPK, immune system, NF-κB, MAPK
Conference Title : ICPIPC 2022 : International Conference on Pediatric Immunology and Pediatric Cardiology
Conference Location : Istanbul, Türkiye
Conference Dates : June 27-28, 2022